IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: R. Dario Norberto CARRARA et al.	Confirmation No. 5916
Application No.: 10/798,111	Group Art Unit: 1616
Filing Date: March 10, 2004	Examiner: K. M. George
For: METHODS AND FORMULATIONS FOR TRANSDERMAL OR TRANSMUCOSAL APPLICATION OF ACTIVE AGENTS	Attorney Docket No.: 88066-7900

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

I, Arnaud Grenier, hereby declare as follows:

1. I am a citizen of France residing at 6, rue des Bergers, Steinbrunn le Haut, F-68440, France, and am one of the named inventors in the subject application. I wish to submit information in support of the Amendment being submitted concurrently herewith.

2. I am familiar with the contents of the office action. I am a pharmacist by training and experience and have a Pharmaceutical Degree in the field of BioPharmacy, from University of Medical and Pharmaceutical Sciences of Clermont Ferrand in 2001. I am currently employed by the assignee of this application and my current title is Head Pharmaceutical Development at ANTARES Pharma.

3. I, in collaboration with my colleagues, discovered and characterized, for the first time, a novel pharmaceutical formulation for efficient transdermal delivery of active agents at therapeutic levels. We tested the effects of this permeation enhancing system on estradiol (the "Antares Gel" formulation), and compared it to a formulation according to Lulla's invention as described in cited US patent application 2004/0213744 (the "Lulla Spray" formulation), and to a third "hybrid" formulation consisting in the spray composition

of Lulla into which was incorporated the permeation enhancing system of the present Antares invention (the "Lulla/Antares Spray" formulation). Compositions are detailed in Table 1 herein after. Results of the 24-hour in vitro permeation study through fresh pig ear skin are summarized in FIG 1 and 2. This study demonstrated that the presently claimed drug carrier comprising an alkanol and combinations of diethylene glycol mono ethyl ether (TRANSCUTOL, "TC") and propylene glycol ("PG") allow for increased transdermal administration of estradiol through the skin. These data clearly show that while enhancement is very variable from one drug to another, the effect of the present permeation enhancing system on maximal drug flux is improved.

Table 1. Composition of the three test formulations

FORMULATION	Antares Gel	Lulla Spray	Lulla/Antares
Composition	% w/w	% w/w	% w/w
17-β-Estradiol hemihydrate*	0.062	0.062	0.062
Ethoxydiglycol (Transcutol P)	5.00	2.00	5.00
Propylene glycol	15.00	4.00	15.00
Ethanol, absolute	48.50	63.94	49.94
Acetone	---	20.00	20.00
Ethylene diamine tetraacetate (EDTA)	0.06	---	---
Triethanolamine (TEA)	0.35	---	---
Carbomer (Carbopol C980)	1.20	---	---
Film former (acrylate copolymer Avalure AC118)	---	10.00	10.00
Purified water	29.88	---	---

FIG. 1. Comparison of relative kinetic profiles of Estradiol

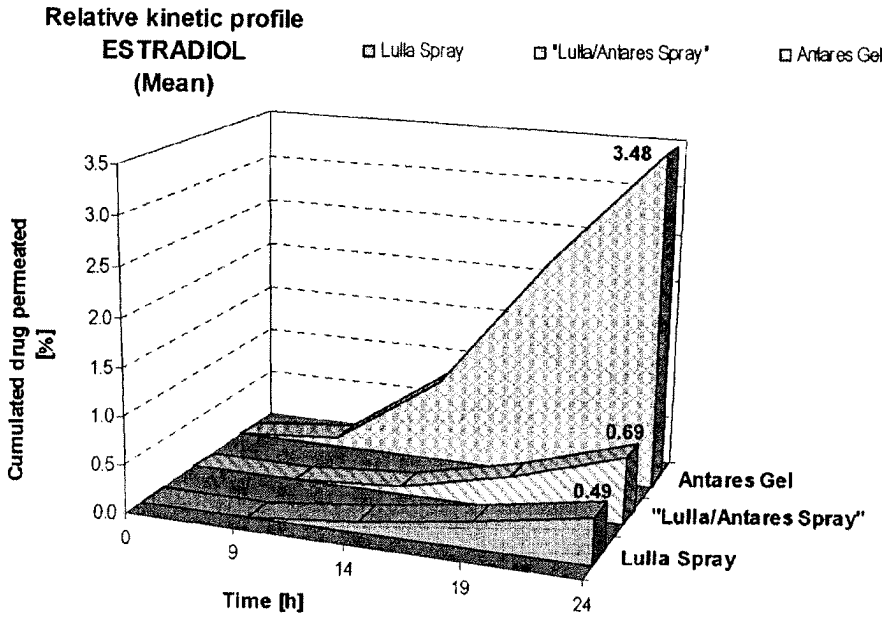
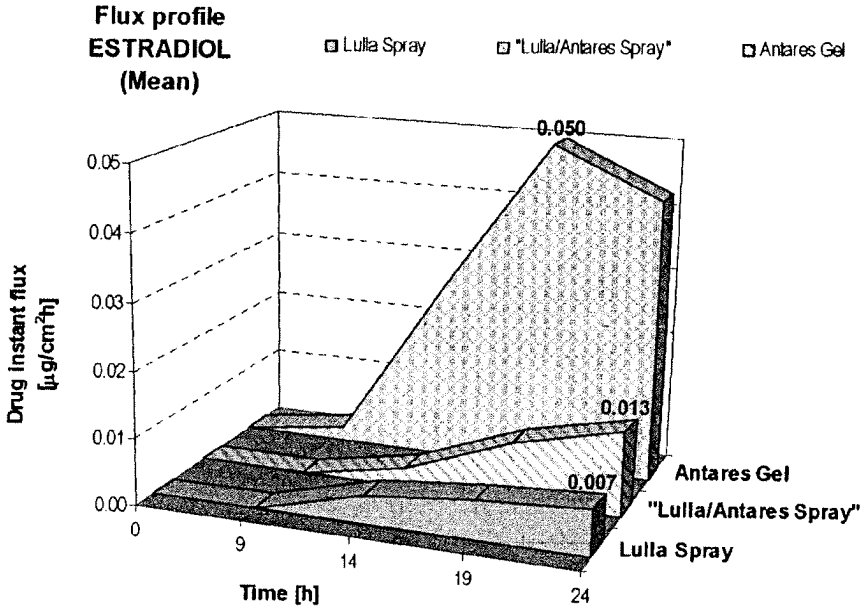


FIG. 2. Comparison of flux profiles of Estradiol



4. I understand that claims 1-16, 20, 21, 27-36, 56-58 and 60 are rejected under 35 U.S.C. 102(e) as being anticipated by over Lulla et al. (US 2004/0213744) for the reasons set forth in of the office action.

Lulla et al. discloses topical composition comprising at least one medicament, film former, solubilizer, permeation enhancer and a plasticizer and its concentrations (paragraph [0023]). Paragraph [0028] teaches examples of the medicinal compounds that can be used of which hormonal steroids are taught. Examples 3,4 and 10-12 teach compositions comprising the hormone estradiol. Preferred solubilizers can be polyhydric alcohols such as propylene glycol (paragraph [0032]). The permeation enhancer can be diethylene glycol monoethyl ether (paragraph [0034]). It is the position of the examiner that the prior art could not possibly list each and every possible combination of PG and TC, however if one of ordinary skill in the art were to use maximum concentrations of TC and PG according to Lulla (6%, respectively 10%, paragraph [0021], then it would fall within the claimed present Antares invention.

The data of the 24-hour in vitro permeation of estradiol presented in FIG 1 clearly show that Antares invention enables to deliver about 7 times more estradiol through the skin than Lulla's invention. Noteworthy, even if addition of Antares Pharma permeation enhancing system at the maximal concentrations (TC 5%, PG 15%) to the volatile alcoholic solvent system of Lulla's invention is responsible for a 40% increase (0.69 versus 0.49) in estradiol delivery, permeated levels of estradiol remain relatively very low in comparison with those achieved thanks to Antares invention (5 times lower actually). Thus this demonstrates that a skill artisan can not achieve the desired results of the Lulla's composition by optimization. Although optimizing ratios of different components might be routine for a skilled artisan, trying to adjust the amounts/ratios of TRANSCUTOL and PG to amounts/ratios that are not suggested or even opposite to the teachings of Lulla are unlikely outcomes. Thus, even if a skilled artisan attempts this optimization, he will not be successful in obtaining the present invention because these references, either alone or in combination, do not disclose the recited amounts nor do they inherently result in the present formulations. Instead, further research and investigation such as that which was conducted by the present inventors would be needed to arrive at the presently claimed components and amounts.

Similar conclusions can be made for skin fluxes of estradiol (FIG 2).

In light of the above, I respectfully believes the present invention is distinct, novel and not anticipated by Lulla et al.

I hereby declare that all statements made herein of my own knowledge and belief are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application and any patent issuing thereon.

Signed this 10th day of July, 2007.

Arnaud Grenier